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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,017	MIGAWA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 37-43* is/are rejected.

7)☒ Claim(s) *35 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election filed on 7/2/03. There are forty-three claims pending and forty-three under consideration. Claims 1-37 are compound claims. Claim 38 is a composition claim. Claims 42 and 43 are use claims. Claims 39-41 are method of synthesis claims. The application concerns some pyranose compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election of Group I in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Objection is made to claims 1-34 and 36-43 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula (I) contains compounds drawn to the non-elected inventions of Groups II-IV.

Claim Objections

4. Claims 35 and 36 are objected to because of the following informalities: All the amide nitrogen atoms (C(O)-N-) in these formulas lack hydrogen atoms. All of the terminal amino groups in structure Ib are drawn with three and not the correct two hydrogen atoms. Appropriate correction is required.

5. Claim 39 is objected to because of the following informalities: There is a missing space after the number "1" in line 1.. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-34 and 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, lines 16-21, 24, 25, page 77 and in lines 2 and 7, page 78, Applicants claim "alkyleno", "heteroalkyleno", "aryleno", heteroaryleno", "halyleno", and "hydroxyleno". What are these radicals? Nowhere in the specification are they defined. In the passage spanning line 24, page 7 to line 8, page 8, Applicants define both "alkyl" and "aryl". Lines 23-25, page defines "heterocycloalkyl" but there is no definition of heteroalkyl. There is a second definition of "alkyl" in lines 16-19, page 11. A second definition of 'aryl" is found in lines 1-3,. A definition of "heteroaryl" is found lines 11-14, page 12. The Examiner suggests using the terms "alkyl", "aryl", "heteroaryl", "halo", and "hydroxyl". The Examiner suggests deleting "heteroalkyleno" and relying upon substituted alkyl, if that is what they intend.

7. Claims 1-34 and 38-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The terms "alkyleno" and "alkyl" in claim 1 is used by the claim to mean "both alkyl and cycloalkyl", while the accepted meaning is "alkyl". The term is indefinite because the specification does not clearly redefine the term. As discussed before there are two different definitions of 'alkyl" in the specification. In the passage spanning line 24, page 7 to line 8, page 6, Applicants state, using open language" that "alkyl" includes cyclic radicals. Cyclohexane is offered as an example. It is art-recognized in organic chemistry that alkyl groups may not be cyclic.

8. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What is "an ~alkyl(heteroyl)" radical? It

is neither defined in the specification nor conventional nomenclature in organic chemistry.

9. Claim 2 recites the limitation "an ~alkyl(heteroyl)" in line 21, page 78. There is no antecedent basis for this limitation in the parent claim 1, which does not mention this radical as a possible value for R_5.

10. Claims 39 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What is the structure of "a reaction-group"? It is not defined in the specification and is not a conventional term in synthetic organic chemistry. The Examiner suggests using the specific radicals intended, being careful to rely upon the specification for support.

11. Claim 42 recites the limitation "claim 39" in line 3. There is no antecedent basis for this limitation in the claim since claim 39 is a synthesis claim. Was claim 38 intended?

12. Claim 43 recites the limitation "prodrug" in line 2. There is no antecedent basis for this limitation in the parent claim 42.

13. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Is the prodrug recited in line 2, a prodrug

of the compounds of formula (I), a prodrug of any second active ingredient, or both?

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In part c) of claim 39, Applicants have the limitation "manipulating said intermediate". What chemical reactions are Applicants intending for this manipulation and where are they described? Since the group "G", which is lost during these manipulations, is also not defined, there is no way for the skilled organic chemist to even guess what reactions Applicants possessed for this process.

15. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bacterial infection, does not reasonably provide enablement for treating every medical condition for which "a desired result" is anticipated. The specification does not enable any physician

skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would treat every human disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with every different human disease, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a huge degree of experimentation. b) There is no direction concerning treating any diseases found in the specification. Applicants describe formulations in the passage spanning line 4, page 15 to line 2, line 30. There are no working examples of any formulation anywhere in this lengthy passage. Applicants do not teach the doses required to practice their invention anywhere in

the specification. Since no compound has ever been used to treat every human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is are *in vitro* assays drawn to 8 bacteria and 1 fungus species described in the passage spanning line 15, page 61 to the end of page 71. None of the tables of data are labeled with the microorganism used, so how is the physician to know which compound to use with which bacteria? A Table 3 is mentioned but is missing from the specification. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts is that no compound has ever been found that will "give a desired result" with every known disease.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the uncounted number of diseases embraced by the claim. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

16. Assuming the word "prodrug" in line 2, claim 43 refers to prodrugs of the compounds of formula (I), then claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. "The factors to be considered in making an enablement rejection have been summarized above. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must

meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large degree of experimentation.

b) There is no direction concerning the prodrugs is found in the specification. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is a major research program must be undertaken to find a single prodrug. f) The artisans required to make Applicants' prodrugs are a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the

hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 37, 38, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Clark (Antibiotica, Ref. 2). The compound Gougerotin fits formula (I) with $R_1 = R_2 = NH_2$, $R_3 = R_4 = R_7 = R_8 = R_9 = R_{11} = R_{12} = R_{16}$ = hydrogen, R_6 = an electron pair, $R_{13} = R_{14}$ = OH, Q = C=O, R_5 = independently hydrogen and the substituted alkyl group $-CH_2$-OH, and R_{15} = the heteroalkeno group propyl with the interior carbon atom replaced by nitrogen. It has Registry Number 56675-45-7 and is found in Fig 2, page 279 of the reference. Applicants have a proviso in lines 11-12, page 78 requiring the number of carbon atoms to be greater than the number of nitrogen atoms in R_5. Since neither of the R_5 radicals contains any nitrogen atoms and one R_5 does not contain any carbon atoms, the conditions of this proviso are satisfied.

The Fisher projection of the sugar shown in Fig 2. shows that the stereochemistry of the two hydroxyl groups on the pyranose ring is defined. Thus,

claim 37 is anticipated. An I.V. LD_{50} in mice is described in the first paragraph on page 278 of the reference. Thus, a parenteral composition was made and Applicants' claim 38 is anticipated. The discussion of the broad spectrum of antibiotic activity and the commercial value of Gougerotin found in paragraph 1, page 278 of the reference means that disease treatment was contemplated and placed into the public domain. Thus, claim 42 is anticipated.

18. Claims 1 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Coutsogeorgopoulos (J. Med. Chem., Ref. 3). The compounds 4a, 4b, 5a, 5b, 5c, and 5d fits formula (I) with $R_1 = R_2 = NH_2$, and $R_1 = NHCH_3$ and $N(CH_3)_2$, $R_3 = R_4 = R_7 = R_8 = R_9 = R_{11} = R_{12} = R_{16}$ = hydrogen, R_6 = an electron pair, $R_{13} = R_{14}$ = OH, Q = C=O, R_5 = independently hydrogen, the substituted alkyl group $-CH_2-$OH, methyl, and both hydrogen, and R_{15} = the heteroalkeno group propyl with the interior carbon atom replaced by nitrogen or ethyl with the terminal carbon replaced by nitrogen. They are found in Chart I, page 772 of the reference. Applicants have a proviso in lines 11-12, page 78 requiring the number of carbon atoms to be greater than the number of nitrogen atoms in R_5. Since neither of the R_5 radicals contains any nitrogen atoms and one R_5 does not contain a carbon atom, the conditions of this proviso are satisfied.

Conclusion

19. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. After February 9, 2004, the Examiner may be reached at (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK